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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: MICROBUBBLE COMPOSITIONS, AND METHODS FOR PREPARING AND USING SAME

(57) Abstract: Described are microbubble compositions including microbubbles having membranes that incorporate modified surface features that may be useful, for example, in facilitating binding to a target surface or substance. The surface features may include non-spherical attributes such as crenations, folds, projections, or wrinkles, which can increase the deformability of the microbubble membrane. Such microbubble compositions can be incorporated into targeted ultrasound contrast agents and methodologies. Methods for preparing modified microbubble compositions include providing microbubbles having spherical membranes, and converting the spherical membranes to non-spherical membranes having surface features as mentioned above. Targeting substances can be incorporated into the membranes before or after their conversion from spherical to non-spherical forms.

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/21712

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 49/00, 9/127; A61B 8/00

US CL : 424/9.51, 9.52, 9.5, 450

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/9.51, 9.52, 9.5, 450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,846,518 A (YAN et al) 08 December 1998 (08.12.1998), see entire document.	1-28, 30-36
Y	US 6,416,740 B1 (UNGER) 09 July 2002 (09.07.2002), see entire document.	1-28, 30-36
Y	US 6,443,898 B1 (UNGER et al) 03 September 2002 (03.09.2002), see entire document.	1-28, 30-36
Y	US 5,869, 538 A (VAN LIEW et al.) 09 February 1999 (09.02.1999), see entire document.	1-28, 30-36
Y	US 6,051,207 A (KLAVERNESS et al) 18 April 2000 (18.04.2000), see entire document.	1-28, 30-36
Y	US 6,224,554 B1 (TICKNER et al) 01 May 2001 (01.05.2001), see entire document.	1-28, 30-36
Y	US 5,464,932 A (ALLCOCK et al) 07 November 1995 (07.11.1995), see entire document.	1-28, 30-36
Y	US 6,187,288 B1 (SCHNEIDER et al) 13 February 2001 (13.02.2001), see entire document.	1-28, 30-36



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

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# INTERNATIONAL SEARCH REPORT

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## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,245,318 B1 (KLIBANOV et al) 12 June 2001 (12.06.2001), see entire document.	1-28, 30-36
Y	US 6,548,048 B1 (CUTHBERTSON et al) 15 April 2003 (15.04.2003), see entire document.	1-28, 30-36
Y	US 6,372,195 B1 (SCHUTT et al) 16 April 2002 (16.04.2002), see entire document.	1-28, 30-36
Y	PRICE ET AL. Delivery of Colloidal Particles and Red Blood Cells to Tissue Through Microvessel Ruptures Created by Targeted Microbubble Destruction With Ultrasound. Circulation. 29 September 1998, Vol. 98, pages 1264-1267, see entire article.	1-28, 30-36

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/21712

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: Claim 29  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claim 29 depends upon claim 38 which is not preceding claim 29.
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

PCT/US03/21712

**Continuation of B. FIELDS SEARCHED Item 3:**

**STN (BIOSCIENCE)**

search terms: gas filled microbubble, liposome, target molecule, crenated, non-spherical, surface projection, converting inventor's names